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STUDY OF CHANGES IN LIPID PROFILE, URIC ACID LEVELS & BP VALUES FOLLOWING THREE MONTHS CONTINUOUS CYCLOSPORIN THERAPY IN PSORIASIS

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ABSTRACT **Objective :** To assess Changes in Lipid profile, Uric acid levels, Serum Potassium levels, BP changes and Hirsutism features following three months Continuous Cyclosporin Therapy in patients with moderate to severe psoriasis. **Methods:** Patients diagnosed as moderate to severe plaque psoriasis and drug naïve to oral Cyclosporin (Diagnosed by NICE Clinical Guidelines) of age between 18-45 years and treated with Oral Cyclosporin 3-5mg/kg/day in 2 divided dose are followed up for the period of three months for the presence and extent of side effects. **Results :** Table shows there is mild increase in systolic BP mean from 127.87 mmHg to 131 mmHg and Diastolic BP mean from 78 mmHg to 82.33 mmHg. Table 3 shows mean total cholesterol level raised from 179.27mg/dl to 202.10 mg/dl, the mean LDL cholesterol value raised from 115.73 mg/dl to 125.23 mg/dl which are statistically significant. The mean TG level raised from 178.37 mg/dl to 125.23 mg/dl. Table 4 shows raise in Hirsutism score from 1.47 to 3.27 which is statistically significant. **Conclusion :** In this study continuous cyclosporine therapy for 3 months in drug naïve psoriasis revealed a significant rise in total cholesterol, LDL cholesterol levels observed in both sexes and significant increase in hirsutism scoring observed in women

KEYWORDS : Cyclosporin, Plaque Psoriasis, BP Changes with Cyclosporin, PASI, Hirsutism.

BACKGROUND

Psoriasis is a chronic inflammatory immune mediated disease of unknown etiology, which is significantly associated with psychological distress and compromised quality of life. Treatment of this condition is not curative but is aimed at inducing a temporary control of clinical manifestations and improving the impact of the disease on quality of life and the level of acceptance of the disease.

The management of a chronic disease like psoriasis is complex and is conditioned by multiple factors, including, but not limited to, the objective severity and distribution of skin lesions, the influence on psychosocial aspects, the response to previous therapies, and the presence of concomitant psoriatic arthritis (PsA) and comorbidities. Therapeutic management of psoriasis usually requires a patient-tailored approach in which combination and sequential therapies are often considered over time in order to augment response, to optimize the safety profile, and/or to meet specific clinical needs. There is a wide armamentarium of therapeutic tools available for the treatment of psoriasis which includes topical medications, phototherapy, and systemic non biological and biological drugs.

It is estimated that moderate-to-severe psoriasis accounts for about 25% of psoriasis patients,[1] most of whom are likely to require systemic drugs or phototherapy. When psoriasis requires systemic therapy, cyclosporine (CsA) is one of the most effective and rapidly acting drugs. Since the time of the first observations documenting the clinical activity of CsA in psoriasis, more than 30 years ago,[2] a considerable amount of clinical data has been accumulated in favour of the efficacy and safety of the drug in many immune mediated skin disorders and especially psoriasis and atopic dermatitis.

In light of the current knowledge and after several years of experience gathered in clinical practice, CsA is often used as first-line therapy in moderate-to-severe forms of psoriasis by several dermatologists.[3] Psoriasis treatment regimens with CsA have to be adapted to the patient's needs and specific characteristics, after an accurate selection and a careful assessment of the risk/benefit ratio.

At doses of 4-5mg/kg/day, CsA is a very active drug, characterized by a rapid onset of response, as demonstrated by the extent and speed of reduction in the Psoriasis Area and Severity Index (PASI) score. A dose of 2.5–3mg/kg/day has a better risk/benefit ratio, with attainment of the highest efficacy in approximately 2-3 months.[4]

The most significant side effects of cyclosporine are nephrotoxicity and hypertension, while other side effects include infection, hyperlipidemia, hyperuricemia, hyperkalemia and gastrointestinal problems. The nephrotoxicity of cyclosporine is both dose- and duration-dependent. According to the literature, lowering the daily dosage (<3 mg/kg) prevents nephrotoxicity. Other studies have investigated renal function and structure in long-term low dose cyclosporine therapy in psoriasis patients and found only mild structural changes (1~2 mg/kg/day for 3.5 years). These side effects could be reduced by using low dose combination therapy.

Cyclosporine

Cyclosporine (cyclosporin A), a cyclic polypeptide consisting of 11 amino acids, is produced by the fungus species Beauveria nivea. Cyclosporine, a potent immunosuppressive, is highly effective in the treatment of psoriasis. Cyclosporine has significant inhibitory effects on the ability of T cells to become activated. However, a direct activity of this drug on human keratinocyte signal transduction or growth has been difficult to demonstrate at relevant concentrations. Nevertheless, treatment of psoriasis or of 12-O-tetradecanoyl phorbol-13-acetate-treated murine skin with cyclosporine does reverse many epidermal abnormalities that are common to these two systems. This suggests that the compound exerts an indirect effect on epidermal keratinocytes in vivo, perhaps through immunocyte inhibition. During treatment of psoriasis patients, cyclosporine therapy resulted in selective changes in the numbers and functions of certain antigen-presenting cell subsets (which were distinct from Langerhans cells) and T-cell subsets. These changes were accompanied by indirect evidence of decreased T-cell lymphokine release. Lesional activity of cyclosporine-treated psoriasis patients was closely correlated with the degree of T-cell activation caused by antigen-presenting cells. Cyclosporine inhibition of lymphokine or cytokine release may result in decreased recruitment of non-Langerhans antigen-presenting cells into the epidermis and thus decreased immunoreactivity in the lesion.[5]

CsA therapy resulted in significant reductions in the absolute number of immune cells (including T cells, monocytes/macrophages, and antigen presenting cells) contained within psoriatic skin. The effect was rapid, with over one-half of the reduction in the density of HLe1+ (human leukocyte antigen-1 positive or bone marrow derived) cells, including T cells, activated T cells, monocytes, and Langerhans cells (LCs), occurring within 3 days.[6]

Dermal CD1+DR+ cells (putative Langerhans cells), which are not found in normal skin but are present in lesional psoriasis skin, were virtually cleared from the papillary dermis after CsA therapy. Although absolute numbers of epidermal Langerhans cells, defined as cells expressing both CD1 (T6) and DR molecules (CD1+DR+), were also reduced after CsA, epidermal non-Langerhans CD1-DR+ cells (macrophages, activated T cells, DR- keratinocytes) demonstrated a proportionally greater decrease, with the ratio of CD1+DR+ Langerhans cells/non-Langerhans CD1-DR+ epidermal cells

changing from a mean of 0.82 at baseline to 1.92 at day.[6]

Cyclosporine can effectively treat severe and disabling psoriasis, and it works quickly. In clinical trials, 80% to 90% of patients who received cyclosporine for 12 to 16 weeks had rapid improvement. [7] The usual initial oral dose is 3 to 5 mg/kg per day given in divided doses.

Here the oral dosage forms given as soft gelatin capsules having a bioavailability of 20% to 50%. After oral administration of cyclosporine, the time to peak blood concentrations is 1.5 to 2 hours. Administration with food delays and decreases absorption. High- and low-fat meals consumed within 30 minutes of administration decrease the AUC by approximately 13% and the maximum concentration by 33%. This makes it imperative to individualize dosage regimens for outpatients. Cyclosporine and its metabolites are excreted principally through the bile into the feces, with only about 6% being excreted in the urine.

Aim

To assess changes in lipid profile, uric acid levels, serum potassium levels, serum creatinine levels, BP Values and hirsutism features following 3 months continuous cyclosporine therapy in patients with moderate to severe psoriasis

MATERIALS AND METHODS

Study Design : Single centric, Prospective, Open labeled, Observational study.

Place Of Study: Dermatology Outpatient Department of Govt Stanley Medical College and Hospital.

Drugs are not administered for the purpose of study. Patients with moderate to severe Plaque Psoriasis as assessed by Static Physicians Global Assessment Six point Scale, and decided for Cyclosporin therapy are recruited for this study.

Study Period: 6 months

Study Duration (Drug Exposure) – Continuous 3 months

Sample Size: 30 patients Completing Continuous oral Cyclosporin therapy

Selection Criteria

Inclusion Criteria

Patients with moderate to severe Psoriasis & drug naïve to oral Cyclosporin.

Age- 18-45 years

Sex- both sexes

Patients who are willing to give informed consent

Exclusion Criteria

Patients with renal impairment

Patients on chronic therapy with drugs with nephrotoxic potential

Known Hypertensive patients, dyslipidaemic patients, gout patients.

Patients on potassium sparing diuretics

Pregnant and lactating women

Known drug hypersensitive reactions

Patients who are not willing to give informed consent.

Methodology

Patients diagnosed as moderate to severe psoriasis (Assessed and treated by Dermatologist) of age between 18-45 years and treated with Oral Cyclosporin 3-5mg/kg/day in 2 divided dose are followed up for the period of 3 months for the presence and extent of side effects.

Potential Side Effects

Nephrotoxicity, Hypertension, Hirsutism, Infection- viral, fungal, bacterial, Hyperlipidemia, Hyperuricemia, Hyperkalemia and Gastrointestinal problems- Abdominal pain, Black tarry stools, Nausea, vomiting, loss of appetite

Follow Up

Every week for first month, once in every 2 weeks for second month and once at the end of 3rd month. (Total visits- baseline visit + 7 visits) Biochemical parameters assessed at monthly interval.

Primary Outcome: To detect and assess the changes in lipid profile, serum creatinine levels, serum potassium, uric acid levels & BP values from baseline and features of hirsutism in females following 3 months continuous Cyclosporin therapy in psoriasis.

Ferrimen Gallwey Scale for hirsutism

Total 9 sites; grading 1-4 for each site.

Score >8 indicates hirsutism, maximum possible score 36.

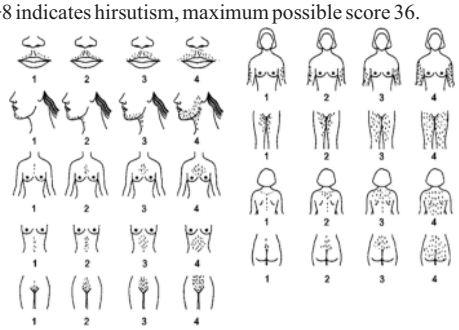


Figure 1: Ferrimen Gallwey Scale for hirsutism

Gingival Hyperplasia Assessment Scale

S.No	Degree of involvement	Description
1	Localized	Limited to gingival in relation to single tooth/ group of teeth
2	Generalized	Involving the gingiva throughout the mouth
3	Marginal	Involvement limited to gingival margins only
4	Diffuse	Involving the gingival margin and the remainder of the gingival mucosa upto muco-buccal fold

Statistics

Statistical analysis done using the software SPSS version 20.0 Variables assessed are mean, Standard Deviation, Standard error, P value.

Test used are Students t test, independent samples test, nonparametric test for intra group analysis, Friedman test.

RESULTS

30 Patients diagnosed as moderate to severe psoriasis (Assessed and treated by Dermatologist) of age between 18-45 years and treated with Oral Cyclosporin 3-5mg/kg/day in 2 divided dose are followed up for the period of 3 months for the presence and extent of side effects. In that male patients contributes 53%, female patients contributes 47%. (Figure 1a). Predominatly 50% of study group belong to 40 to 50 years of age. (Figure 1b)

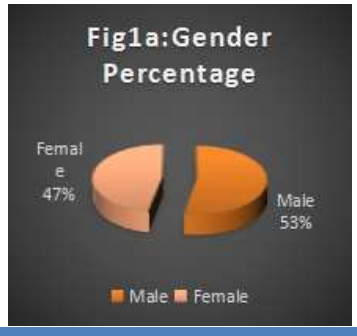
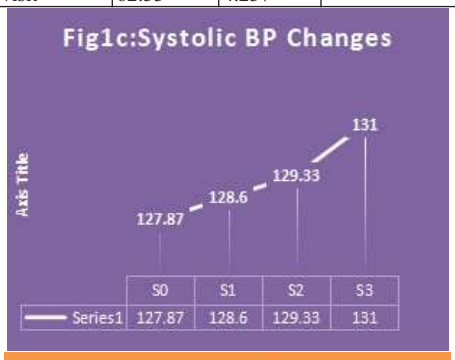


Table 1 represents the mean changes in the Systolic and Diastolic Blood Pressure during the 3 months of study period. Even though there is rise in systolic and diastolic blood pressure, but it is not statistically significant. Similarly change in blood parameters like Urea, Creatinine, serum potassium has been seen during the study period, but it is not statistically significant. (Table-2)

Table-1 Changes In Blood Pressure

Parameters	Mean	SD	P value
SBP 0 visit	127.87	6.907	>0.05 (not significant)

SBP 1 visit	128.60	7.318	
SBP 2 visit	129.33	7.208	
SBP 3 visit	131.00	6.142	
DBP 0 visit	78.00	4.871	>0.05 (not significant)
DBP 1 visit	78.80	4.766	
DBP 2 visit	81.40	4.673	
DBP 3 visit	82.33	4.237	



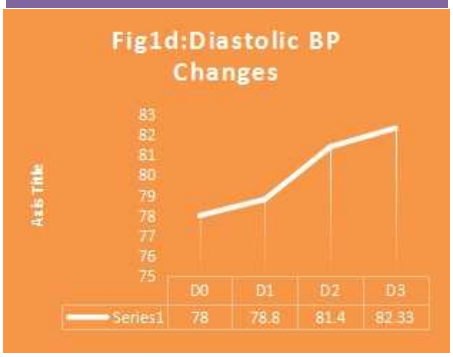
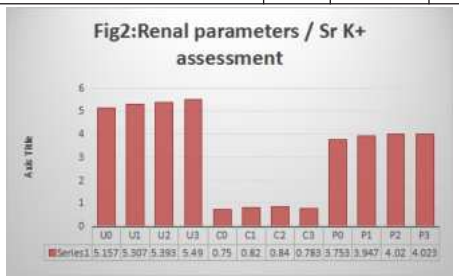


Table-2 Changes In Blood Parameter

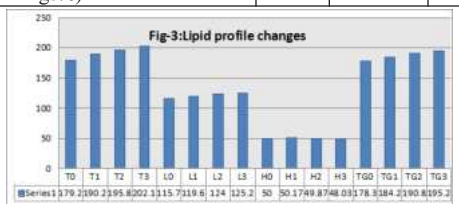
Blood Parameters	Mean	Standard Deviation	P value
Urea (mgs%) 0 visit	5.157	1.4207	>0.05 ,not significant
U1 (mgs%) at the end of 1st month	5.307	1.4553	
U2 (mgs%) at the end of 2nd month	5.393	1.4888	
U3 (mgs%) at the end of 3rd month	5.490	1.4537	
C0 (Creatinine in mgs%) 0 visit	0.75	0.1676	>0.05 ,not significant
C1 (mgs%) at the end of 1st month	0.82	0.1648	
C2 (mgs%) at the end of 2nd month	0.84	0.1610	
C3(mgs%) at the end of 3rd month	0.783	0.1783	
P0 (Potassium-mEq/L) 0 visit	3.753	0.2209	>0.05 ,not significant
P1 (Potassium-mEq/L) at the end of 1st month	3.947	0.3350	
P2 (Potassium-mEq/L) at the end of 2nd month	4.02	0.3408	
P3 (Potassium-mEq/L) at the end of 3rd month	4.023	0.3491	



During the study period , the mean changes observed in Total cholesterol and LDL cholesterol were statistically significant (Table-3) and the level were raised from the baseline values. Also the blood levels of HDL cholesterol reduced from baseline values, but it is not statistically significant. Similarly there was a rise in triglyceride levels from the baseline values , but it is not statistically not significant.

Table-3 Changes In Blood Cholesterol Level Over 3 Months

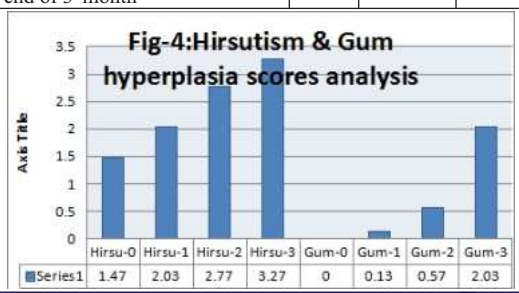
Lipid profile	Mean	Standard Deviation	P value
T0 (total cholesterol in mg% baseline)	179.27	12.188	<0.05 (significant)
T1(total cholesterol at the end of 1st month in mgs%)	190.27	23.867	
T2(total cholesterol at the end of 2nd month in mgs%)	195.83	18.439	
T3 (total cholesterol at the end of 3rd month in mgs%)	202.10	22.099	
L0 (LDL cholesterol at 0 visit in mgs%)	115.73	10.017	<0.05 (significant)
L1 (LDL cholesterol at the end of 1st month in mgs%)	119.67	10.453	
L2 (LDL cholesterol at the end of 2nd month in mgs%)	124.00	11.129	
L3 (LDL cholesterol at the end of 3rd month in mgs%)	125.23	11.524	
H0 (HDL cholesterol at 0 visit in mgs%)	50.00	4.799	>0.05 (not significant)
H1 (HDLcholesterol at the end of 1st month in mgs%)	50.17	5.018	
H2 (HDLcholesterol at the end of 2nd month in mgs%)	49.87	5.131	
H3 (HDL cholesterol at the end of 3rd month in mgs%)	48.03	4.222	
TG0 (Triglyceride at 0 visit in mgs%)	178.37	18.630	>0.05 (not significant)
TG1 (Triglyceride at the end of 1st month in mgs%)	184.23	20.900	
TG2 (Triglyceride at the end of 2nd month in mgs%)	190.80	22.907	
TG3 (Triglyceride at the end of 3rd month in mgs%)	195.27	25.321	



There were appearance of features of Hirsutism in the female patients at the end of 3 months has been observed which was statistically significant. There is no significant changes observed in Gum hyperplasia in the study population. (table-4)

Table-4 Ferrimen Gallwey Scale For Assessing Hirsutism & Gingival Hyperplasia Assessment Scale

Clinical parameters	Mean	Std Deviation	P value
Hirsu-0 Hirsutism score at 0 visit	1.47	1.795	<0.05 (significant)
Hirsu-1 Hirsutism-score at the end of 1st month	2.03	2.484	
Hirsu-2 Hirsutism- score at the end of 3rd month	2.77	3.441	
Hirsu-3 Hirsutism score at the end of 3rdmonth	3.27	4.051	
Gum-0 Gum-Hyperplasia score at 0 visit	0	.000	>0.05 (not significant)
Gum-1 Gum-Hyperplasia score at the end of 1stmonth	0.13	.346	
Gum-2 Gum-Hyperplasia score at the end of 2ndmonth	0.57	.504	
Gum-3 Gum-Hyperplasia score at the end of 3rdmonth	2.03	.964	



DISCUSSION

The changes in lipid profile, uric acid levels, serum potassium levels, serum creatinine levels, Blood pressure values and hirsutism features were followed up and assessed following 3 months continuous cyclosporine therapy in patients with moderate to severe psoriasis.

Table 1, Figure 1c and figure 1d represents the changes in blood pressure in all patients, that showed a raise in mean blood pressure after the end of 3 months, but is not statistically significant. There is increase in urea levels, creatinine levels, serum potassium levels at the end of cyclosporine therapy, but not statistically significant.

50 percentage of the study population belongs to the age group between 30 to 40 years, 26.70 percentage of study population are above 40 years. With regard to renal parameter changes, which were not affected much during this 3 months therapy in this study population.

Table3 & figure 3 represent the changes in lipid profile, which showed statistically significant raise in total cholesterol and LDL cholesterol levels.

Hirsutism features were assessed in female patients using Ferrymen Gallwey scale, which shoed a significant raise in the score.

The study spanned for a period of 6 months to get the target sample number. 45 patients were recruited and enrolled in the study. At the end of first month 10 patients lost follow up. At the end of 2 months of continuous therapy 5 patients wanted to go to their native place and continue treatment at the district Govt hospitals and hence values and assessment for the last month couldn't be done.

This is a review of the side effects of Cyclosporin A (CyA) in patients with severe psoriasis; In particular, paraesthesia, hypertrichosis, gingival hyperplasia and gastrointestinal disorders may occur, but are generally transient, mild to moderate in severity and only rarely require discontinuation of CyA[8].

Although most of these changes were not clinically relevant, laboratory monitoring of patients with psoriasis treated with CyA is essential.

Limitation

Cyclosporin therapy for treatment of psoriasis is usually should not exceed continuous one year. If needed and if dermatologist conclude cyclosporin therapy can be given continuously for two years provided strict clinical and biochemical monitoring of these patients is feasible.

In this study continuous 3 months cyclosporine therapy alone cannot conclude or dispute presence or absence of possible side effect in drug naïve psoriasis patients.

Continuous follow up for one to two years during therapy and follow up for detection of late side effects during drug free period after completing one or two years of cyclosporine therapy is needed to detect side effects of cyclosporine in psoriasis..

CONCLUSION

In this study continuous cyclosporine therapy for 3 months in drug naïve psoriasis revealed that there is no significant changes in blood pressure, renal parameters, serum potassium levels, HDL cholesterol and Triglyceride levels but significant rise in total cholesterol, LDL cholesterol levels observed in both sexes and significant increase in hirsutism scoring observed in women. No significant changes in gum hypertrophy scoring.

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